**Final Study Report**

**Study Title:** *Effect of norepinephrine infusion on hepatic blood flow during goal-directed hemodynamic therapy.*

**EudraCT number**: *2018-004139-66*

**Eudamed number:** *NA*

**Study protocol code:** *AGO/2018/006*

**ClinicalTrial.gov identifier:** *NCT03965117*

Sponsor: *UZ Ghent*

Coordinating Investigator: *Dr. Jurgen. Van Limmen*

Funder: *N.A.*

Date of report: *2022-08-07*

Name and signature Sponsor:

Date signature Sponsor: .....

Table of content

1. Introduction

Maintaining adequate blood pressure is important for survival of organs. Recent studies have demonstrated that higher blood pressures were necessary for prevention of acute kidney injury and myocardial injury after non-cardiac surgery. Hypotension after induction and maintenance of anesthesia is common. For maintaining adequate blood pressure in a euvolemic patient, vasopressor therapy is required. Norepinephrine (NOR) is commonly used to treat anesthesia-related hypotension. The hepatic circulation has many alpha- and beta-adrenergic receptors and is very sensitive for adrenergic stimulation such as norepinephrine infusion. Animal studies (Hiltebrand et al.)[1] suggest that NOR has only minimal effect on hepatic blood flow however the effect of NOR on hepatic blood flow in clinical surgical patients remains unclear.

The aim of the study is to evaluate the effect of NOR on hepatic blood flow during.
goal directed hemodynamic therapy.

2. Objectives of the study

2.1 Primary objectives

Primary objective of the study is to assess the effect of norepinephrine infusion (NOR) on hepatic blood flow and hepatic vascular pressures during goal-directed hemodynamic therapy. We hypothesize that NOR reduces total hepatic blood flow and increases hepatic vascular pressures.

2.2 Secondary objectives

Secondary objective of the study is to evaluate the effects of NOR on systemic vascular resistance (SVR), portal venous resistance (PVR), cardiac index (CI), blood loss and total fluid administration.

3. Investigational Medicinal Product

Noradrenaline (Norepinephrine) Aguettant 1 mg/ml, vials of 4 ml. Solution to be made: 3 mg/ 50 ml NaCl 0,9%. Max dose: 0.06mg/kg/h during max 10h. Glass vial of 4 ml, 1mg/ml, administration was done intravenously.

Producer:

DELPHARM Tours

Rue Paul Langevin 37

170 Chambray-Les-Tours

France

Distribution:

AGUETTANT SA NV

B.D.C.

Esplanade 1 BP 61

B-1020 Brussels

4. Study Protocol Summary

### 4.1 Inclusion criteria

- Adult ≥ 18 years ≤ 80 years (female or male)
- ASA I – II – III
- Able to comprehend, sign and date the written informed consent document to participate in the clinical trial.
- Patient is scheduled for pancreatic surgery.

### 4.2 Exclusion criteria

- Allergy to the medication.
- Renal insufficiency (SCr > 2 mg/dL).
- Severe heart failure (EF < 25%).
- Hemodynamic instable patients.
- Atrial fibrillation.
- Sepsis.
- BMI > 40.
- Severe coagulopathy (INR > 2).
- Thrombocytopenia (< 80 x $10^3$ /mcL).
- End stage liver disease.
- Pregnancy and breastfeeding women

### 4.3 Primary endpoint

Evaluation of the effect of NOR on hepatic blood flow and pressures during goal-directed hemodynamic therapy.

Time point of evaluation:

- T1 – after pancreatectomy at baseline MAP
- T2 – after pancreatectomy, after reaching target MAP 10 – 20% above baseline (T1).
- T3 – before surgical reconstruction and after reaching target MAP 20 – 30% above baseline (T1).

### 4.4 Secondary endpoints

Evaluation of the effect of NOR on systemic vascular resistance (SVR), portal venous resistance (PVR), CI, blood loss en fluid administration.

Time point of evaluation:

- T0 – after incision and opening of the abdominal cavity.
- T1 – after pancreatectomy at baseline MAP
- T2 – after pancreatectomy, after reaching target MAP 10 – 20% above baseline (T1).
- T3 – before surgical reconstruction and after reaching target MAP 20 – 30% above baseline (T1).
- T4 – before closure of the abdominal cavity.

A minimum of 5 minutes between flow measurements is advisable.

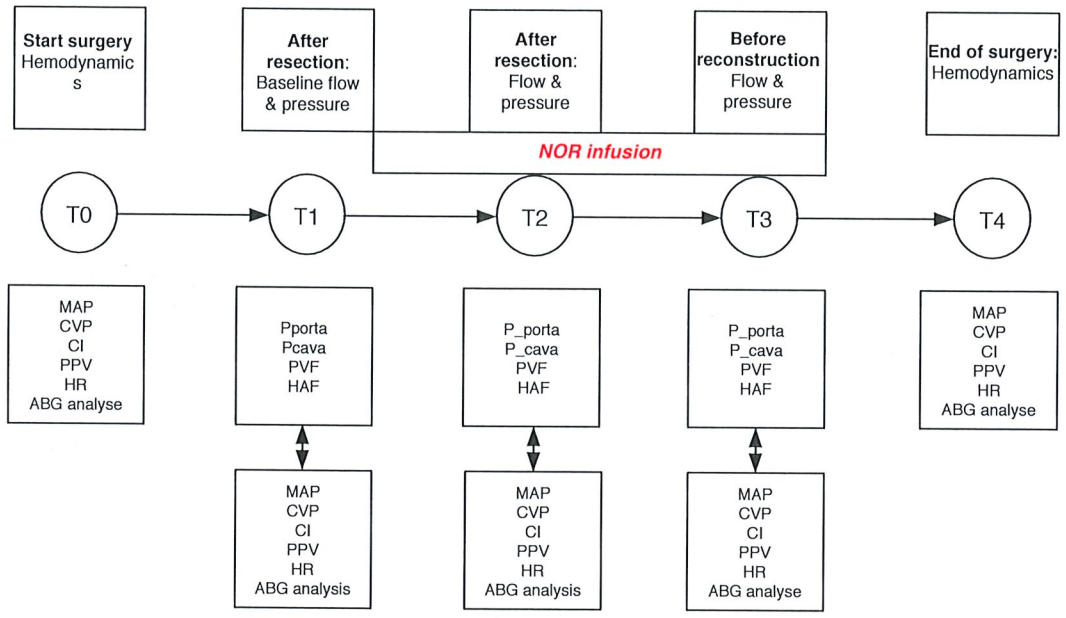
### 4.5 Procedures

All patients receive standardized anesthesia care for pancreas surgery according to the existing departmental protocol for these interventions.
Anesthesia is induced and maintained using propofol and remifentanil. For tracheal intubation, rocuronium 1 mg/kg is used for neuromuscular blockade. During surgery and before every experimental measurement an additional bolus of rocuronium is administered (standard of care). Depth of anesthesia will be measured using Bispectral Index (BIS) Monitoring (BIS$^{TM}$, Covidien, MA, USA) which is standard of care for pancreas surgery. Propofol will be titrated to obtain a BIS value between 40 – 60, which is an adequate depth of anesthesia for surgery. For propofol, target controlled infusion model is used (Schnider model, effect-site concentration). For opioids, remifentanil, target controlled infusion is used (Minto model, effect site concentration). All patients receive individualized goal-directed haemodynamic therapy based on the transpulmonary thermodilution technique.
Mechanical ventilation is standardized in all patients. After lung recruitment, tidal volume is set at 8 – 10 ml/kg ideal body weight, with a respiratory rate 14 – 16 per minute and PEEP 5 $cmH_2O$. Mechanical ventilation is adjusted according to the arterial blood gas values.
Haemodynamic measurements will be performed using the transpulmonary thermodilution technique. After placement of a central venous catheter, a 4 or 5 Fr PiCCO catheter is placed in the left femoral artery. Hemodynamic data are recorded using PulsioFlex (Maquet, Getinge Group, Germany), at designated times. Hemodynamic variables will be recorded. These include:

- Heart rate (bpm)
- Central venous pressure (mmHg)
- Mean arterial pressure (mmHg)
- Cardiac index (L/min/m$^2$)
- Pulse pressure variation (PPV)

Measurements of the hepatic flow will be done using ultrasound transit time flow measurements (TTFM) (Medi-Stim, AS, Oslo, Norway). Different probe sizes will be used, according to the size of the vessel (range 2 – 12 mm). Hepatic flow will be measured in the hepatic artery (HAF) and portal vein (PVF). Simultaneously, pressure measurements will be obtained in portal vein ($P_{Porta}$) and caval vein ($P_{Cava}$) using a 25-gauge needle which is directly placed in the vein. Both flow and pressure will be simultaneously recorded (VeriQ, Medi-Stim AS, Oslo, Norway). To minimize the effect of ventilation on pressure, these measurements will be obtained during apnea.
At designated times, arterial blood gas measurements will be drawn and analyzed. Cumulative fluid and vasopressor administration will be recorded at the time of measurement.
After incision and opening of the abdominal cavity, start hemodynamic measurements are recorded (T0). A baseline flow measurement will be performed after pancreatectomy (T1). The second flow measurement (T2) will be performed after pancreatectomy, after reaching target MAP 10 – 20% above baseline. The last flow measurement (T3) will be performed after reaching target MAP 20 – 30% above baseline and before surgical reconstruction. Before

closure of the abdominal cavity hemodynamic variables are once again recorded (T4). Between each flow measurement there will be a minimum of 5 minutes.
NOR will be started at 0,1 mcg/kg/min and titrated according to its hemodynamic effect. After baseline MAP (which is > 60 mmHg), NOR is targeted according to baseline MAP. At T2, MAP is between 10 – 20 % above baseline (T1), at T3 MAP is between 20 – 30 % above baseline (T1).




NOR will be administered according to its hemodynamic effect:

- T0 & T1 MAP > 60 mmHg
- T2 MAP 10 – 20 % above baseline (T1)
- T3 MAP 20 – 30 % above baseline (T1)
- T4 MAP > 60 mmHg

Following parameters will also be registered during every measurement :

- BIS
- Urine output
- Amount of fluids administered (crystalloids – colloids)
- Dose of NOR
- Dose of dobutamine (if administered)
- Dose of propofol administered
- Dose of remifentanil administered

Preoperative parameters (blood pressure, heartrate,…) that are registered on the ward as part of the standard of care, will also be used.

Postoperative blood results from the day of surgery and the 1st day after surgery, as part of the standart of care, will be used as well.

### 4.6 Randomisation and blinding

Not relevant.

## 5. Study analysis

For sample size calculation, a previous pilot trial with similar methodology was used [2]. Based on this publication, a 15% reduction in HAF and PVF was considered clinically significant. G*Power 3.1.9.2[3] was used to calculate the sample size. For an alpha error of 5% and a beta error of 20%, we necessitated 28 patients to detect a flow reduction of 15%. We used linear mixed modelling to compare HBF, HAF and PVF at the 3 study points. Patient identity was used as random effect (random intercept), to account for the repeated measures. The study points were used as fixed effect. Logarithmic transformation was used to meet the assumption of normal distribution of the residuals. To assess a potential effect of the concomitant administration of SOMATO on the effect of NE, a post hoc analysis was performed. Patients were divided based on presence (Group S, n = 20) or absence (Group NS, n = 8) of SOMATO administration. The statistical model was updated by adding these groups as interaction factor to the fixed effect. All statistical tests were performed using R (version 3.3.3)[4]. Lme4-package (v 1.1-23) and car-package (v 3.0-9) were used for linear mixed modelling and to determine the optimal transformation within the Box-Cox family, respectively.

## 6. Independent Ethics Committee and Competent Authority

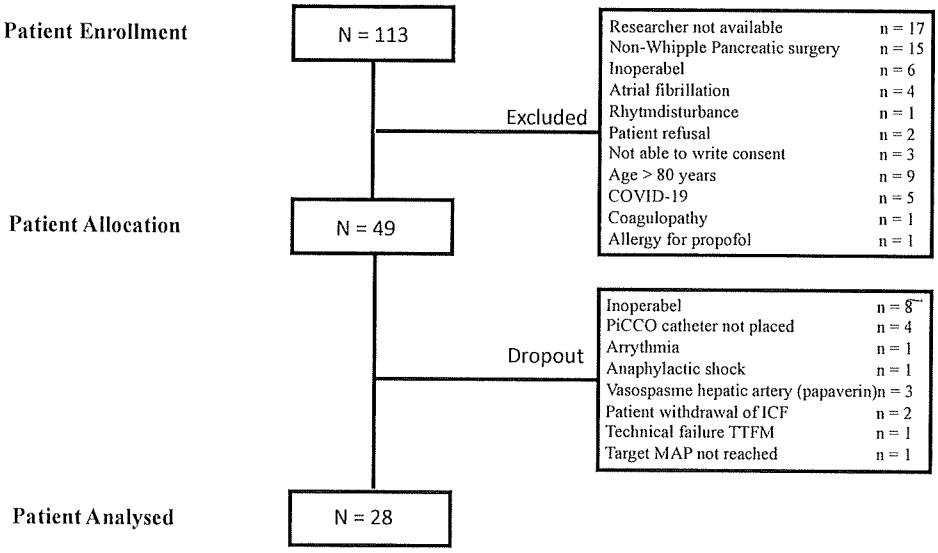
| **OVERVIEW APPROVED DOCUMENTS** | | |
|---|---|---|
| **Initial submission :**<br>- Protocol v 1 dd. 2019-02-21<br>- Summary of protocol v 1 dd. 2019-02-21<br>- SmPC Noradrenaline dd. SEP/2018<br>- SmPC NaCl dd. Dec/2014<br>- Informed consent form v 1 dd. 2019-02-25<br>- CRF v 1 dd. 2019-02-20<br>- CE certificate Medi-Stim probe dd. 2018-05-03<br>- Label v 1 dd.2018-09-09 | **Approval date central EC:**<br>**2019-04-11** | **Approval date FAMPH:**<br>**2019-04-11** |
| **Notification 1:**<br>- CRF v1.1 dd. 2019-05-20 | **Approval date central EC: NA** | **Approval date FAMPH : NA** |
| **Amendment 2:**<br>- Protocol version 1.1 dd.2020-02-11<br>- ICF version 2.0 dd.2020-02-11 | **Approval date Central EC:**<br>**2020-04-21** | **Approval date FAMPH: NA** |

| Amendment 3:<br>- Protocol version 1.2 dd.2020-04-27<br>- ICF version 3.0 dd.2020-04-27 | Approval date Central EC:<br>2020-06-12 | Approval date FAMPH: NA |
|---|---|---|

7. Results

7.1 Subject enrollment and demographics

Between 2019-05-28 and 2020-10-19 a total of 113 patients were screened for eligibility. Registration of the first patient (number 01) was done on 2019-05-29. A total of 49 patients were included of which 21 dropped out. Dropouts were replaced.




Demographics are expressed in table 1:

| | Group (n = 28) | Group S (n = 20) | Group NS (n =8) |
|---|---|---|---|
| Male / Female ratio | 14 / 14 | 9/11 | 5/3 |
| Age (years) | 58 (13) | 56 (13) | 62 (12) |
| Length (cm) | 170 (8.2) | 170 (8.6) | 171 (7.5) |
| Weight (kg) | 72.5 (13.0) | 74.6 (13.2) | 67 (11.5) |
| BMI | 25.0 (3.8) | 25.9 (3.6) | 22.8 (3.5) |
| Systolic BP (mmHg) | 129 (18) | 131 (19) | 123 (17) |
| Diastolic BP (mmHg) | 76 (8) | 72 (7) | 78 (8) |

| | | | |
|---|---|---|---|
| MAP (mmHg) | 94 (10) | 96 (10) | 89 (9) |
| HR (bpm) | 75 (10) | 72 (10) | 80 (10) |
| ASA I / II / III | 2 / 19 / 7 | 1 / 14 / 5 | 1 / 5 / 2 |
| Smoker (F / N / Y) | 9 / 11 / 8 | 7 / 7 / 6 | 2 / 4 / 2 |
| Beta-blocking agent (Y / N) | 2 / 26 | 1 / 19 | 1 / 7 |
| ACE-inhibitor (Y / N) | 4 / 24 | 2 / 18 | 2 / 6 |
| Duration of surgery (min) | 567 (84) | 575 (75) | 548 (107) |

Data are expressed in mean (SD). Body mass index (BMI), mean arterial blood pressure (MAP), heart rate (HR), American Society of Anesthesiologist physical status (ASA).

Intraoperative characteristics are expressed in table 2:

| | **Total Group (n = 28)** | **Group S (n = 20)** | **Group NS (n = 8)** |
|---|---|---|---|
| Crystalloids (ml) | 4184 (1594) | 4197 (1539) | 4151 (1836) |
| Crystalloids ($ml.kg^{-1}.h^{-1}$) | 6.1 (1.6) | 5.9 (1.6) | 6.6 (1.7) |
| Colloids (ml) | 182 (288) | 165 (313) | 225 (225) |
| Estimated blood loss (ml) | 342 (220) | 339 (240) | 350 (175) |
| Urinary Output (ml) | 790 (445) | 762 (381) | 859 (602) |
| Urinary Output ($ml.kg^{-1}h^{-1}$) | 1.2 (0.7) | 1.1 (0.7) | 1.3 (0.6) |
| Ephedrine (mg) | 10.5 (7.9) | 9.3 (8.0) | 13.5 (7.5) |
| Phenylephrine (mcg) | 0.27 (0.31) | 0.24 (0.33) | 0.34 (0.28) |
| Propofol (mg) | 3886 (997) | 4052 (938) | 3470 (1082) |
| Propofol ($mg.kg^{-1}.h^{-1}$) | 5.7 (0.8) | 5.7 (0.9) | 5.6 (0.6) |
| Remifentanil (mcg) | 4575 (1420) | 4797 (1479) | 4022 (1164) |
| Remifentanil ($mcg.kg^{-1}.min^{-1}$) | 0.11 (0.02) | 0.11 (0.02) | 0.11 (0.03) |
| Duration of surgery (min) | 567 (84) | 575 (75) | 548 (107) |

Data are expressed in mean (SD)

7.2 Study specific results

Primary objective:

NE dose-dependently reduced $HAF_i$ in both groups. For $PVF_i$ however, effects of NE differed between group S and group NS. Patients receiving SOMATO had a significantly lower $PVF_i$ at T1, which remained unchanged with NE, while in group NS, NE decreased $PVF_i$. Because of these alterations, also total $HBF_i$ decreased with NE. NE significantly decreased conductance in both groups, indicating its effect on the vascular tone of the hepatic artery. The PI of both vessels remained identical. Caval and portal pressures remained unchanged with NE in both groups.

Results are expressed in table 3:

| Variable | Timepoint | Total Group (n = 28) | Group S (n = 20) | Group NS (n = 8) |
|---|---|---|---|---|
| Total HBF indexed (ml $min^{-1}$ $m^{-2}$) | T1 | 548 (182) | 511 (168) | 640 (191) |
| | T2 | 465 (149)# | 447 (153)# | 508 (138)# |
| | T3 | 458 (144)# | 454 (145)# | 467 (149)# |
| Relative Total HBF (% of CO) | T1 | 17.8 (5.7) | 16.7 (5.6) | 20.4 (5.4) |
| | T2 | 15.2 (4.6)# | 14.7 (4.9)# | 16.3 (3.8)# |
| | T3 | 14.6 (4.3)# | 14.6 (4.5)# | 14.7 (4.0)# |
| HAF indexed (ml $min^{-1}$ $m^{-2}$) | T1 | 215 (118) | 216 (128) | 212 (95) |
| | T2 | 163 (83)# | 162 (82)# | 164 (92)# |
| | T3 | 142 (70)# | 150 (79)# | 124 (41)# |
| Relative HAF (% of CO) | T1 | 6.9 (3.6) | 7.0 (3.9) | 6.8 (3.0) |
| | T2 | 5.3 (2.7)# | 5.3 (2.5)# | 5.3 (2.9)# |
| | T3 | 4.6 (2.3)# | 4.8 (2.6)# | 3.9 (1.3)# |
| Conductance HAF (ml $min^{-1}$ $m^{-2}$ $mmHg^{-1}$) | T1 | 3.0 (1.8) | 3.0 (1.9) | 3.0 (1.4) |
| | T2 | 1.9 (1.0)# | 1.9 (0.9)# | 2.0 (1.1)# |
| | T2 | 1.6 (0.8)# | 1.6 (0.9)# | 1.3 (0.4)# |
| PVF indexed (ml $min^{-1}$ $m^{-2}$) | T1 | 333 (137) | 295 (109)* | 429 (161)* |
| | T2 | 302 (117) | 285 (109) | 344 (133)# |
| | T3 | 315 (120) | 304 (109) | 344 (151)# |
| Relative PVF (% of CO) | T1 | 10.9 (4.5) | 9.8 (4.0)* | 13.7 (4.8)* |
| | T2 | 9.9 (3.7) | 9.4 (2.5) | 11.1 (3.8)# |
| | T3 | 10.0 (3.5) | 9.7 (3.3) | 10.8 (4.2)# |
| Portal Pressure (mmHg) | T1 | 10 (5) | 9 (5) | 11 (5) |
| | T2 | 11 (5) | 10 (5) | 12 (5) |
| | T3 | 10 (5) | 9 (5) | 12 (6) |
| Caval Pressure (mmHg) | T1 | 7 (4) | 6 (3) | 8 (4) |
| | T2 | 6 (4) | 6 (4) | 6 (4) |
| | T3 | 7 (4) | 7 (4) | 6 (4) |
| PI Portal Vein | T1 | 0.6 (0.4) | 0.7 (0.5) | 0.5 (0.3) |
| | T2 | 1.2 (2.3) | 1.4 (2.7) | 0.7 (0.4) |
| | T3 | 0.6 (0.3) | 0.6 (0.3) | 0.6 (0.3) |
| PI Hepatic Artery | T1 | 1.2 (0.5) | 1.3 (0.6) | 1.0 (0.4) |
| | T2 | 1.5 (0.5) | 1.6 (0.5) | 1.4 (0.5) |
| | T3 | 1.5 (0.7) | 1.6 (0.6) | 1.4 (0.8) |

Data are expressed in mean (SD). Hepatic blood flow (HBF), hepatic arterial blood flow (HAF), portal vein blood flow (PVF), pulsatility index (PI). Significant differences are marked as * for significant between group difference and # for significant within group difference, compared to T1 ($p < 0.05$).

Secondary objective:

NE significantly increased MAP and SVRi, similarly in both groups. CI, CVP, HR, PVRi, Pms and Eh remained unchanged. NE infusion was started after T1 measurements and increased to 0.06 mcg $kg^{-1}$ $min^{-1}$ (SD 0.03 mcg $kg^{-1}$ $min^{-1}$) at T2 and 0.101 mcg $kg^{-1}$ $min^{-1}$ (SD 0.05 mcg $kg^{-1}$ $min^{-1}$) at T3. All patients met the pre-defined hemodynamic targets and none of the patients necessitated NE before experimental measurements. Both ephedrine and phenylephrine were used to counteract post-induction hypotension (respectively 10.5 mg (SD 7.9 mg) and 270 mcg (SD 310 mcg). All patients were hemodynamically stabilized by the time of the first measurement.

Results are expressed in table 4:

| **Variable** | **Time-Point** | **Total group (n = 28)** | **Somatostatin** | |
|---|---|---|---|---|
| | | | **Yes (n = 20)** | **No (n = 8)** |
| MAP (mmHg) | T1 | 73 (10) | 73 (11) | 72 (7) |
| | T2 | 84 (10)# | 85 (11)# | 83 (7)# |
| | T3 | 93 (12)# | 93 (13)# | 92 (10)# |
| HR (bpm) | T1 | 78 (11) | 77 (11) | 80 (11) |
| | T2 | 75 (11) | 74 (11) | 78 (10) |
| | T3 | 75 (12) | 75 (13) | 75 (10) |
| CVP (mmHg) | T1 | 5 (3) | 5 (3) | 5 (4) |
| | T2 | 5 (3) | 5 (3) | 6 (4) |
| | T3 | 5 (3) | 5 (3) | 6 (4) |
| CI ($L.min^{-1}.m^{-2}$) | T1 | 3.1 (0.5) | 3.1 (0.6) | 3.1 (0.4) |
| | T2 | 3.1 (0.5) | 3.1 (0.6) | 3.1 (0.3) |
| | T3 | 3.2 (0.5) | 3.2 (0.6) | 3.2 (0.3) |
| SVRI ($dyn.sec.cm^{-5}.m^{-2}$) | T1 | 5698 (775) | 5729 (844) | 5621 (613) |
| | T2 | 6574 (820)# | 6624 (895)# | 6448 (628)# |
| | T3 | 7235 (963)# | 7260 (1039)# | 7172 (798)# |
| PVRi ($dyn.sec.cm^{-5}m^{-2}$) | T1 | 1.4 (1.4) | 1.5 (1.5) | 1.2 (1.1) |
| | T2 | 1.7 (1.9) | 1.8 (2.1) | 1.4 (1.1) |
| | T3 | 1.4 (1.4) | 1.2 (.09) | 1.9 (2.2) |
| Pms (mmHg) | T1 | 12 (3) | 12 (3) | 12 (3) |
| | T2 | 13 (3) | 13 (3) | 13 (4) |
| | T3 | 13 (3) | 13 (3) | 14 (3) |
| Eh | T1 | 0.63 (0.20) | 0.64 (0.19) | 0.63 (0.23) |
| | T2 | 0.62 (0.18) | 0.62 (0.16) | 0.62 (0.22) |

| | | | | |
|---|---|---|---|---|
| | T3 | 0.63 (0.16) | 0.63 (0.16) | 0.61 (0.17) |
| PPV | T1 | 10 (3) | 10 (3) | 11 (4) |
| | T2 | 9 (3) | 8 (3) | 10 (4) |
| | T3 | 8 (3) | 8 (3) | 8 (3) |
| pH | T1 | 7.32 (0.06) | 7.31 (0.06) | 7.34 (0.07) |
| | T2 | 7.31 (0.05) | 7.31 (0.05) | 7.33 (0.06) |
| | T3 | 7.31 (0.05) | 7.30 (0.05) | 7.32 (0.06) |
| Lactate ($mmol.L^{-1}$) | T1 | 1.3 (0.8) | 1.4 (0.9) | 1.1 (0.4) |
| | T2 | 1.3 (0.8) | 1.4 (0.9) | 1.1 (0.4) |
| | T3 | 1.3 (0.8) | 1.4 (0.9) | 1.1 (0.3) |
| Noradrenaline ($mcg\ kg^{-1}\ min^{-1}$ | T1 | 0 (0.01) | 0 (0.01) | 0 (0.01) |
| | T2 | 0.06 (0.03)# | 0.05 (0.03)# | 0.06 (0.04)# |
| | T3 | 0.101 (0.05)# | 0.102 (0.06)# | 0.100 (0.05)# |

Data are expressed in mean (SD). Mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), cardiac index (CI), systemic vascular resistance indexed (SVRI), mean circulatory filling pressure (Pms), heart performance (Eh), pulse pressure variation (PPV). Significant differences are marked as * for significant between group difference and # for significant within group difference, compared to T1 ($p < 0.05$).

8. Safety

No SAE`s were reported during this trial period.

9. Protocol deviations

No major protocol deviations occurred during this trial period.

10. Discussion and overall conclusions

The results of the current study show that in hemodynamically optimized patients, administration of NE resulted in significantly reduced total HBF which was mediated by both a reduction in HAF and PVF. This response seemed to be influenced by the administration of SOMATO. SOMATO-treated patients had a lower PVF at baseline and administration of NE in these patients, leads to a reduction of total HBF primarily by a reduction of HAF while PVF remained low and unchanged.

We choose pancreaticoduodenectomy as experimental model for this study because – in contrast to liver surgery – this type of surgery is standardized without potential anticipated hemodynamic disturbances. Additionally, there is an easy access to hepatic vasculature during the procedure, which allowed us to perform direct flow measurements of HBF. No previous human studies have used direct

flow measurements in assessing the effect of NE on HBF. TTFM was used, which is very reliable and considered to be the "gold standard" for measuring blood flow[5].

Recent studies emphasize the importance of maintaining adequate blood pressure to prevent postoperative organ failure[6, 7]. Heart, brain and kidney have a robust autoregulation, in which the intrinsic regulatory mechanism provides adequate blood flow despite fluctuations in blood pressure[8], while in the liver, this autoregulatory protection mechanism is weak[9].

NE is frequently used as vasopressor to counteract hypotension during high-risk surgery or critically ill patients[10, 11]. It is used to improve systemic hemodynamic variables, but less attention is given to the potential important effects of NE on regional blood flow.

NE could play a dual role, improving systemic hemodynamic variables but affecting regional HBF. Previous animal studies have shown that NE improves cardiac output and venous return by recruitment of unstressed volume into stressed volume[12–14]. Small human studies in septic patients have confirmed this[15]. The volume status of the patient seems to be of particular importance for this effect, as it was primarily observed in hypervolemic patients who received higher dosage of NE[1, 14]. In our study, such finding was not observed, and CI remained unchanged. This may be the consequence of the fact that our patients were already hemodynamically optimized with low filling pressures and a balanced volume status. Consequently, to increase the MAP to our target, only small dosages of NE were necessary to obtain the desired effect. Therefore, dosages of NE may have been too low to observe substantial systemic hemodynamic effects. The optimal target for intra-operative MAP is still under debate[6, 7]. The target MAP used in this study, was higher than routinely used in clinical practice but was in the range of the preoperative MAP value. A previous study suggested that target blood pressure is probably best based on the preoperative blood pressure of each individual patient[10].

The effect of NE on splanchnic circulation is puzzling and not yet fully understood. NE affects both systemic and regional hemodynamic variables but the clinical effect of NE on splanchnic vasculature depends on different factors. Relative density of $\alpha_1$-, $\alpha_2$- and $\beta_2$-adrenorecptor in the splanchnic vasculature, the dosage of NE, the pre-existing sympathetic tonus of the splanchnic vasculature and the blood volume in the splanchnic circulation all may play a crucial role to predict the effect of NE[16].

NE affects the splanchnic vascular resistance sites, which are scattered all over the pre-portal arterial, hepatic arterial and portal venous vasculature[16, 17]. Changes in vascular tone, by increasing resistance, results in a decreased conductance and decreased blood flow[9, 18]. Previous animal studies have shown that NE infusion results in a reduction of total HBF[19], by reducing both HAF and PVF[19, 20]. A small human study confirmed these results[21]. However, another experimental study failed to observe any effect on HBF when NE was used to correct hypotension[1]. Our in vivo study confirmed the results of previous animal studies[19, 20]. Indeed, NE resulted in a reduction of total HBF and due to the weak autoregulatory mechanism, blood flow was not maintained during fluctuations in blood pressure[8, 9]. Thus, the effect of NE on HBF seems to be complex and remains ill-defined.

The effects of NE on hepatic circulation seem to be influenced by the concomitant administration of SOMATO. A total of 20 patients received - on surgical indication – SOMATO, to reduce pancreatic secretions, and protect pancreaticoduodenal anastomosis. Besides reducing pancreatic secretions, SOMATO also induces a mesenterial vasoconstriction[22]. PVF is determined by the outflow of blood from the mesenteric organs and as a result, SOMATO treated patients had a lower PVF[23, 24]. Our study confirmed this finding, as patients receiving SOMATO, had lower PVF at baseline, compared with other patients. Interestingly, although PVF is lower at baseline, these patients do not have higher HAF as would be expected with the hepatic artery buffer response. This effect can buffer up to 70% of the reduced PVF but ultimately this buffer response seems to become exhausted and HAF returns to normal values[25–28]. As SOMATO is given before pancreatectomy at the start of the operation, a possible explanation would indeed be that the buffer response to SOMATO-induced decrease in PVF has faded away, ultimately resulting in the normalization of HAF. Of note, in the SOMATO-treated

patients, NE administration did not further reduce PVF, contrary to what was observed in patients not receiving SOMATO, and the reduction of total HBF was primarily related to a reduction in HAF. The precise underlying reasons for this different response are not clear and the present study does not allow to further elucidate this issue.

The results of the current study show that modulating blood pressure with vasopressors such as NE may substantially alter HBF. These findings underscore the importance of considering also potential effects on regional tissue blood flow. Although NE improves systemic hemodynamics it may profoundly affect regional blood flow.

Conclusion:

In hemodynamically optimized patients NE improves systemic hemodynamics but impairs HBF. SOMATO interacts with this mechanism. In the presence of SOMATO, NE has a similar net effect on HBF, but the underlying mechanism of reduced blood flow differ.

11. References

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